REMARKS

Amendments in the claims

Claims 1-2, 10-13 and 15-25 are pending.

Per the Examiner's suggestion, Claim 25 is amended herein to include formal Markush language.

Claims 1 and 25 are amended herein to clarify that the claimed drug in the microreservoirs is in free base form. This amendment is supported throughout the specification as filed, for example, at pg. 3, lines 13-14 which states that "an amine functional drug in its free base form has been incorporated."

No new matter is added, and no change in inventorship is believed to occur, as a result of any amendment herein.

RESPONSE TO OFFICE ACTION DATED 27 APRIL 2010

1. Rejection under 35 U.S.C. §103(a) over Chien and Gale

Claims 1-2, 10-11 and 17-24 stand rejected under 35 U.S.C. §103(a) over US Patent No. 5,788,983 to Chien *et al.* (herein "Chien") in view of US Patent No. 4,588,580 to Gale *et al.* (herein "Gale"). This rejection is respectfully traversed.

Claim 1, as amended herein recites:

> A transdermal delivery system (TDS) comprising a self-adhesive matrix containing a self-adhesive polymer and microreservoirs containing an amine-functional drug in free base form selected from the group consisting of fentanyl and oxybutynin, wherein the microreservoirs are within the self-adhesive matrix and have a maximum diameter less than the thickness of the self-adhesive matrix and wherein the self-adhesive matrix is permeable to the amine-functional drug in free base form, and the self-adhesive matrix is substantially impermeable to the amine functional drug in protonated form.

Chien, the primary document relied upon, reports a transdermal dosage unit for administration of one or more pharmaceuticals, particularly a combination of progestational and estrogenic steroids, simultaneously at controlled and variable rates of transdermal delivery.

Gale reports a system comprising a backing member, a release liner, and a drug reservoir/contact adhesive layer having fentanyl dissolved in, and if desired, dispersed therethrough.

1.1 Failure to teach all elements

It is respectfully submitted that a presumption of *prima facie* obviousness has not been established at least because the alleged combination fails to teach all elements of Claim 1. Particularly, Chien and Gale do not disclose, teach or suggest the following elements recited in Claim 1:

1. *"microreservoirs containing an amine-functional drug in free base form"*

Although Chien provides a large laundry list of possible drugs, including broad classes of drugs, that may or may not work in Chien's dosage unit, Chien makes no mention or differentiation of drugs being in free base form versus protonated form, nor specifically "microreservoirs containing drugs in free base form". Gale does not cure this deficiency either. In contrast to Chien and Gale, Applicant's dosage unit was specifically designed to improve transdermal drug delivery of weakly basic amines.

2. *"the microreservoirs...have a maximum diameter less than the thickness of the self-adhesive matrix"*

Neither Chien nor Gale teach that the maximum diameter of microreservoirs should be less than the thickness of the matrix. The pending Office Action dated 27 Apr 2010 states at p. 8: "Regarding the claimed limitation that the maximum diameter is less than the thickness of the self-adhesive matrix, it is taught that the microreservoirs are dispersed in the polymeric adhesive. Since they are dispersed therein, their corresponding diameter would be less than the thickness of the matrix." This conclusion is mistaken. Just because microreservoirs are dispersed in a matrix does not mean that their maximum diameter is less than the thickness of the matrix. Microreservoirs can be dispersed throughout a matrix but still come into contact with the outer edge of the matrix, and thus come into contact with the skin. Whereas, if the maximum diameter of the microreservoirs is less than the thickness of the matrix, this avoids contact of the free base drug with the skin. This is an important feature of Applicant's microreservoirs which took a great amount of experimentation to determine and achieve. It is an important feature because one wants to avoid having the free base drug come in direct

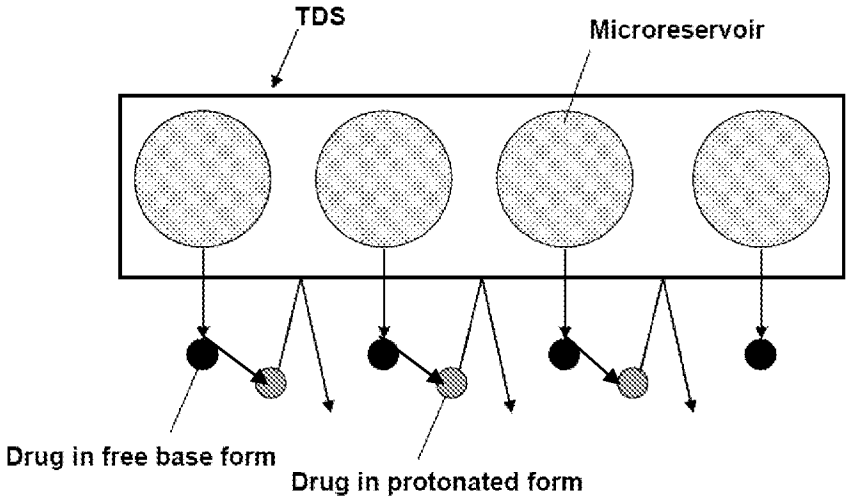
contact with slightly acidic skin which causes protonation of the free base and unwanted back diffusion of the drug. This structural element of Claim 1 and concept is not taught anywhere in Chien or Gale.

3. *"the self-adhesive matrix is permeable to the amine-functional drug in free base form"*

Applicant's self-adhesive matrix must be permeable to the amine-function drug in free base form. As Chien does not mention the free base form of drugs, Chien therefore cannot teach a matrix being permeable to amine-functional drugs in free base form. This element of Claim 1 is also not taught by Gale.

4. *"the self-adhesive matrix is substantially impermeable to the amine functional drug in protonated form"*

Applicant's self-adhesive matrix must also be substantially impermeable to the amine functional drug in protonated form. This is in order to help limit back diffusion of the amine-functional drug. Indeed, this semi-permeability of Applicant's TDS is not disclosed, taught or suggested by Chien or Gale. For clarity: below is an exaggerated schematic of Applicant's claimed semi-permeability characteristics:



5. *Applicant's matrix functions as both adhesive and permeability control as required by Applicant's Claim 1*

Lastly, Applicant's Claim 1 requires the free base drug to be embedded in a matrix which is both adhesive (*i.e.* self-adhesive matrix) and provides the permeability control. In contrast, Chien uses a permeability regulating polymer which is separate from the drug layer.

Chien even states in prosecution that "[t]he present invention is a transdermal dosage unit having an impervious backing layer and a reservoir layer having a reservoir compartment region and an outer wall. The reservoir compartment region contains a liquid medium in which one or more pharmaceuticals are dissolved. The outer wall of the reservoir layer is a permeability-regulating polymer membrane..." *See* Chien response to Office Action dated 2 April 1996 at passage bridging p. 5-6, emphasis in original.

1.2 Chien is not enabling

Further, it is respectfully submitted that a presumption of *prima facie* obviousness has not been established at least because Chien, the primary document relied upon, is not enabled. Although Chien provides a laundry list of possible drugs and classes of drugs at Col 11, clearly the ordinary artisan would not believe that each drug mentioned and each drug in each class mentioned would work in Chien's dosage unit. More importantly, the ordinary artisan would find it incredible that every drug in each class mentioned would work in Applicant's claimed dosage unit, which had to be specifically developed for weakly basic amine drugs in free base form. In support of this conclusion:

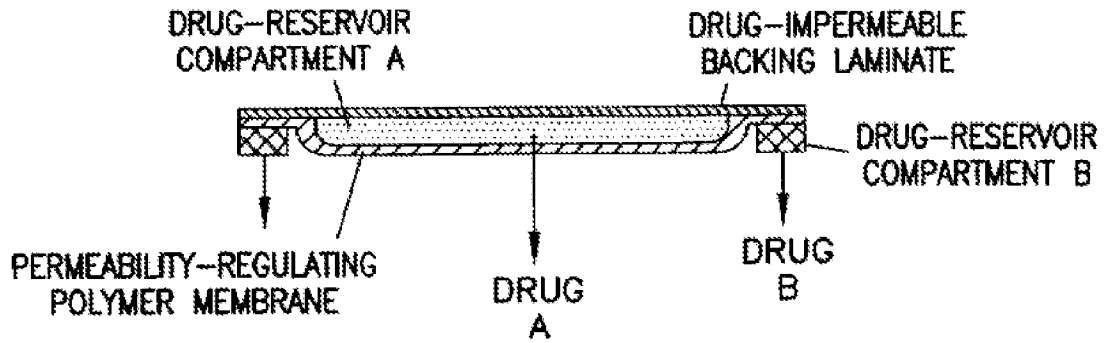
- First, all the examples in Chien are directed to hormone drugs. Almost the entire description is directed to these hormone drugs, and mostly in combination, except for the laundry list at Col 11. There is not even any mention of the effects of free base vs. protonation has on drug delivery. In fact, many of the drugs in Chien's laundry list are salts (hydrochlorides) and thus are charge neutral. They do not have a pair of uncoupled electrons and thus would not work in Applicant's TDS. If anything, Chien may represent a mere invitation to experiment with the different classes of drugs. It is well known that such invitation does not establish a *prima facie* case obviousness and the amount of experimentation that would need to be done from a reading of Chien is clearly undue.
- Second, even the US Examiner during prosecution of the Chien patent recognized that Chien's disclosure was not enabling for all the drugs he attempted to claim and thus Chien had to amend his claims to a limited

Markush group of hormone drugs in order to obtain allowance. Please see Chien Final Office Action dated 20 March 1997 and Chien's response dated 28 May 1997.

1.3 Chien did not even recognize the problem, much less provide any reasonable guidance toward Applicant's claimed TDS

Further, it is respectfully submitted that a presumption of *prima facie* obviousness has not been established at least because an ordinary artisan reading Chien does not find any reasonable guidance on how to improve transdermal drug delivery of weakly basic amine drugs in free base form, and moreover how to arrive at Applicant's claimed TDS to solve this problem. Applicant respectfully submits that when making an obviousness determination "[a] prior art reference must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention" See MPEP 2141.03 (emphasis in original). When read "as a whole", Chien represents an extremely broad disclosure and reports an abundance of embodiments, most of which lead away from Applicant's TDS. Below is just an example of a number of selections an ordinary artisan would have to make reading Chien to arrive at Applicant's claimed TDS:

(1) Chien's dosage unit can comprise mono- or multi-regional reservoir compartments. One would have to select mono-regional which goes against Chien's focus on multi-regional reservoir compartments and Chien's focus on simultaneous administration of hormone drugs to achieve a synergistic effect. Below is the exemplified embodiment in Chien (Fig. 1):



(2) One also has to select between macroreservoirs and microreservoirs;

(3) If one selects microreservoirs (which do not appear to be defined by Chien), one would also have to select between an adhesive polymer, elastomeric polymer or gelling polymer;

(4) One would then have to select an amine-functional drug in free base form which is not reported anywhere in Chien; and

(5) Determine an adhesive polymer that can provide the claimed semi-permeability (*i.e.* be permeable to the drug in free base form and substantially impermeable to the protonated form)

Clearly, this constitutes too many compounded, sequential selections from a vague disclosure to teach Applicant's claimed TDS. Where is the guidance to make any one of these specific selections to lead an ordinary artisan to Applicant's Claim 1, especially in view of Chien's focus on a multi-component TDS? Gale surely provides no guidance as Gale does not even mention microreservoirs. In this case such a multi-step selection, without any guidance on which selections to make, clearly constitutes an unreasonable amount of hindsight using guidance from Applicant's specification to arrive at the claimed invention. It is apparent that in the instant case, "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." In re O'Farrell, 853 F. 2d 894, 903 (Fed. Cir. 1988). "In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." In re Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2009), *emphasis added.*

1.4 No motivation to modify Chien

When read "as a whole", Chien focuses on a TDS system comprising at least four distinct elements – see Chien's Figure 1 reproduced above. To arrive at the claimed invention, it would be necessary to modify Chien's TDS to be a system comprising a monolithic component that does at least three different functions or, alternatively, to single out one component, *e.g.,* compartment B, to be combined with Gale. However, one of ordinary skill in

the art would not have been motivated to use just "drug-reservoir compartment B" in Chien because such use would not achieve the goal of Chien, *i.e.,* simultaneous administration of multiple pharmaceuticals. Thus, it would not have been obvious to separate "drug-reservoir compartment B" from the TDS of Chien and modify the separated "drug-reservoir compartment B" with the teaching of Gale in order to arrive at a TDS of Claim 1.

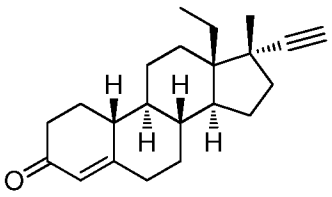
It should be noted that Chien describes throughout the specification two key structural features: (1) that its TDS is designed to administer multiple pharmaceuticals, and (2) "drug-reservoir compartment B" is integrated into the TDS. For example, Chien states in Col. 2, lines 20-24 that "it is desired to provide improved methods of administration of pharmaceuticals, including the simultaneous administration of multiple pharmaceuticals with different pharmacological activities" To meet this goal, one would need to use the entire TDS described by Chien, *i.e.*, a TDS having at least two drug-reservoir compartments, each of which containing a pharmaceutical with a different pharmacological activity. Furthermore, "drug-reservoir compartment B" comprises an adhesive which is necessary for the proper functioning of the TDS, and thus, is an integral component to the system. Neither of these two Chien key features are recited in Applicant's claims. Therefore, it would not have been obvious for a person having ordinary skill in the art to modify Chien to a system comprising a single self-adhesive matrix containing microreservoirs with an amine-functional drug in free base form, wherein the self-adhesive matrix functions as both an adhesive and permeability controller. For at least this further reason, a presumption of *prima facie* obviousness has not been established for Claim 1 over Chien and Gale.

1.5 Lack of combinability

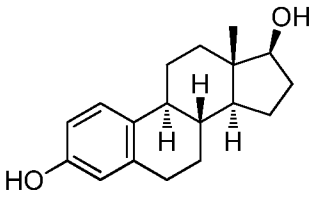
Lastly, there is no motivation to combine Chien and Gale. The Examiner asserts at page 8 of the present Office Action that the TDS of Chien can be used for analgesics, thus motivating a person having ordinary skill in the art "to utilize fentanyl base when desiring to deliver an analgesic transdermally". This observation is respectfully traversed. The term "analgesics" is a generic term encompassing a broad spectrum of pain killers which involves various modes of action and chemistry. The term itself does not provide any information about drug permeability which is a key feature in Claim 1, and thus, it would not be sufficient

to motivate a person having ordinary skill in the art to combine the teachings of Chien and Gale.

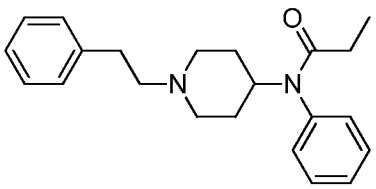
It is even clearer when the compounds described in Chien and Gale are considered. As can be seen from the structures drawn below, levonogestrel and estradiol have a very different chemical make-up from that of fentanyl:



Levonorgestrel



Estradiol



Fentanyl

Levonorgestrel and estradiol are both steroids and do not have any nitrogen-containing functional groups capable of having an uncoupled electron pair, characteristic of amine. Neither levonorgestrel nor estradiol have protonatable groups that could form a protonated, salt form. On the other hand, fentanyl is non-steroidal and contains a tertiary amine and an amide. Fentanyl can form a free base (shown above) or a protonated, quaternary ammonium salt, a feature lacking in each levonorgestrel and estradiol.

Gale describes "a contact adhesive layer having the drug [fentanyl] dissolved in, and if desired, dispersed therethrough" (Col. 6, lines 48-50). However, Gale fails to describe microreservoirs and provides no motivation for dispersing fentanyl throughout the adhesive matrix. For example, Gale states that "while this system can be employed to provide drug delivery rates within the ranges described herein, the actual delivery rate cannot be as precisely controlled as would be with the systems described generally in FIGS. 1 and 2", which depict a TDS with a pouch-like macroreservoir and a multilaminate type TDS, respectively (Col. 6, lines 54-59, emphasis added). At least because of the different physico-chemical properties of steroids compared to fentanyl and the teachings of Gale, it would not have been obvious to one having ordinary skill in the art to combine Chien and Gale. For at least this further reason, a presumption of *prima facie* obviousness has not been established for Claim 1 over Chien and Gale.

1.6 Conclusion

The alleged combination fails to teach microreservoirs containing an amine-functional drug in free base form within a self-ahesive matrix that is permeable to the amine-functional drug in free base form and substantially impermeable to the amine-functional drug in protonated form. Furthermore, there is no suggestion or motivation to modify and/or combine Chien or Gale to provide a TDS with all the elements of Claim 1. Thus, a presumption of *prima facie* obviousness has not been established, and Claim 1 is not obvious over Chien in view of Gale.

Claims 2, 10-11, and 17-24 embody all the features of Claim 1 by depending therefrom directly or indirectly and these claims are nonobvious over Chien in view of Gale at least for the same reasons as Claim 1 is nonobvious. Thus, withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

2. Rejection under 35 U.S.C. §103(a) over Chien and Muller

Claim 25 stands rejected under 35 U.S.C. §103(a) over Chien in view of WO 99/49852 to Muller *et al*. (herein "Muller"). This rejection is respectfully traversed.

Claim 25 as amended herein recites:

> A TDS comprising a self-adhesive matrix containing a self-adhesive polymer and microreservoirs containing an amine-functional drug in free base form selected from the group consisting of aminotetralin compounds, wherein the microreservoirs are within the self-adhesive matrix and have a maximum diameter less than the thickness of the self-adhesive matrix; and wherein the self-adhesive matrix is permeable to the amine-functional drug in free base form, and the self-adhesive matrix is substantially impermeable to the amine-functional drug in protonated form.

Muller reports a transdermal therapeutic system comprising a non-aqueous acrylate or silicone polymer adhesive and (-)-5,6,7,8-tetrahydro-6-propyl(2-(2-thienyl)-ethyl)amino)-1-naphthol (rotigotine).

It is respectfully submitted that a presumption of *prima facie* obviousness has not been established because (1) the alleged combination fails to teach all elements; and (2) the

teaching of Chien and Muller are not properly combinable. The rationale presented in Section 1 of this response is also relevant to the present rejection.

The alleged combination of Chien in view of Muller fails to teach all elements of Claim 1. As shown in Section 1.1 of this response, Chien fails to teach microreservoirs containing an amine-functional drug in free base form within a self-adhesive matrix which is permeable to the amine-functional drug in free base form but is substantially impermeable to the amine-functional drug in protonated form. Although Muller does report rotigotine (an amine-functional drug), Muller does not mention a TDS with microreservoirs containing free base drug less than the thickness of a matrix, and the matrix having the claimed semi-permeability and therefore does not cure this deficiency.

Furthermore, due to the different physico-chemical properites of steroids compared to rotigotine, it would not have been obvious to one having ordinary skill in the art to combine the TDS of Chien with the rotigotine of Muller to obtain a TDS of Claim 25.

Lastly, similar to Chien and Gale discussed above, there is no suggestion or motivation to combine Chien or Muller to provide a TDS comprising microreservoirs containing an amine-functional drug in free base form in a self-adhesive matrix that has the claimed permeability characteristics. Neither Chien nor Muller provides any guidance that Applicant's microreservoirs would be able to provide a high-steady state flux of amine-functional drug and prevent back diffusion. Thus, a presumption of *prima facie* obviousness has not been established, and Claim 25 is not obvious over Chien in view of Gale. Therefore, withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

3. Rejection under 35 U.S.C. §103(a) over Chien, Gale and Pfister

Claims 12 and 13 stand rejected under 35 U.S.C. §103(a) over Chien in view of Gale and in further view of U.S. Patent No. 5,232,702 to Pfister *et al.* (herein "Pfister"). This rejection is respectfully traversed.

Claims 12 and 13 depend directly or indirectly from Claim 1, and thus include all features of Claim 1. The present rejection over Chien in view of Gale and Pfister has the same issues as the combination of Chien and Gale discussed above in Section 1 of this response. Pfister does not teach or suggest microreservoirs containing an amine-functional drug in free

base form selected from the group consisitng of fentanyl and oxybutynin in a self-adhesive matrix which is permeable to the amine-functional drug in free base form and substantially impermeable to the amine-functional drug in protonated form. Thus, the deficiencies of the alleged combination of Chien and Gale are not supplemented by Pfister.

For at least these reasons, a presumption of *prima facie* obviousness has not been established for Claims 12 and 13 over the alleged three-way combination. Thus, withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

4. Rejection under 35 U.S.C. §103(a) over Chien, Gale and Lipp

Claims 15 and 16 stand rejected under 35 U.S.C. §103(a) over Chien in view of Gale and in further view of U.S. Patent No. 5,676,968 to Lipp *et al.* (herein "Lipp"). This rejection is respectfully traversed.

Claims 15 and 16 depend directly or indirectly from Claim 1, and thus include all features of Claim 1. The present rejection over Chien in view of Gale and Lipp has the same issues as the combination of Chien and Gale discussed above in Section 1 of this response. Lipp does not teach or suggest microreservoirs containing an amine-functional drug in free base form selected from the group consisting of fentanyl and oxybutynin within a self-adhesive matrix which is permeable to the amine-functional drug in free base form and substantially impermeable to the amine-functional drug in protonated form. Thus, the deficiencies of the alleged combination of Chien and Gale are not supplemented by Lipp.

5. Conclusion

At least for these reasons, Claims 15 and 16 are not obvious over the alleged combination. Thus, withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the Application is in condition for allowance.

If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

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